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BIOEFFECTS DATA CONCERNING THE SAFE USE OF GAAS LASER TRAINING --ETC(U)
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BIOEFFECTS DATA CONCERNING THE SAFE USE OF GaAs LASER TRAINING DEVICES (U)

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Modern weaponry poses a vexing problem to the military training community: how can realistic battlefield games be conducted which mimic the undeniable ability of weaponry to produce lethal action at a distance? A child's pointed "BANG, you're dead!" suffers in that it has an unverifiable effect, is limited in range, and exposes the originator to immediate retaliation by the target. It does, however, contain the essential ingredients of a weapons simulation system; the ability to engage a target and transmit a message which can be interpreted by the target in terms of its subsequent ability to function. A key aspect of the message is that it implies a fatal hit but *does not possess* that element of real lethality.

Systems have been devised which simulate the firing of live munitions for training purposes. The MILES system, developed by PM TRADE, is an example. A gallium arsenide (GaAs) laser transmitter is mounted on, and boresighted with, each weapon, and all potential targets are equipped with detectors sensitive to GaAs laser radiation. When a weapon is triggered, no projectile is fired; rather a signal is transmitted from the laser and directed at the intended target. The success of the round is scored upon receipt of the signal at the target. The system is effective; however it does present a new problem. The MILES system transmits laser beams at personnel; the probability of their eyes being exposed is high. It is essential that the consequences of such ocular exposure be understood to insure that the signal used for simulation does not carry potential harm.

Within the Army, safety restrictions on the use of all lasers are governed by the provisions of laser safety standards, AR 40-46 and TBMED 279 (1,2). In a quest for effectiveness, the designers of MILES have pushed the emitted power to the maximum permissible exposure (MPE) allowed by the standards. An understanding of the potential hazard of the MILES system can be gained by testing the accuracy of the provisions of the safety standards.

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TBMED 279 dictates the MPE for laser viewing as a function of several laser parameters including wavelength, exposure duration, effective irradiance diameter and repetitive pulse factors. The relative values of the MPE were derived from bioeffects data which related the potential for tissue alteration to the operational characteristics of the laser. The eye is the most vulnerable part of the body to visible and near infrared laser radiation. This is true because within the eye a light absorbing layer of tissue (retina) lies at the focus of the eye lens system. Just as the rays of the sun can be concentrated by a lens to burn wood, so is a laser beam concentrated onto the retina where the concentrated energy can induce thermal, mechanical, and chemical processes which alter the retinal tissue.

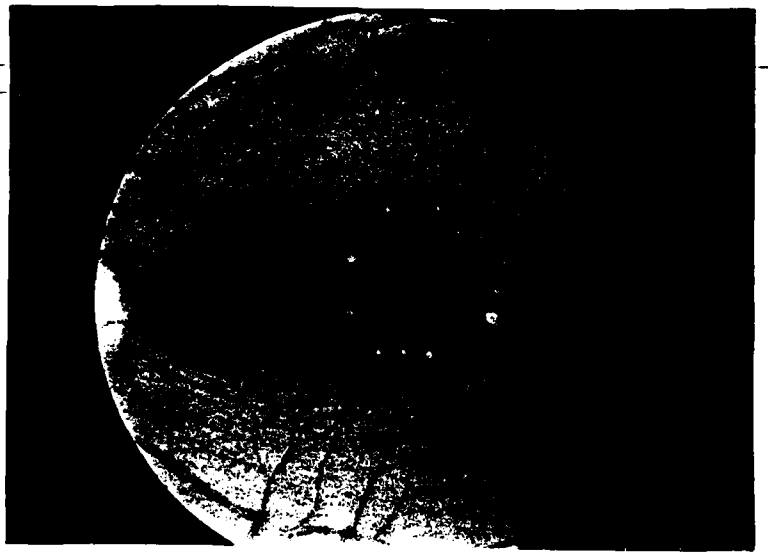

FIGURE 1. Rhesus monkey retina with laser-induced damage.

The MPE has, for the most part, been based upon the ED_{50} for visible retinal alteration in rhesus monkeys under a given set of exposure conditions. What does that mean? Figure 1 is a photograph of the retina of a live rhesus monkey. The retina is the thin layer of tissue at the back of the eye which contains the visual photodetectors. Damage to the retina can diminish vision. The relatively dark circle near the center is the macula, the area of central vision, and in the center of the macula lies the fovea, the area of most acute vision. Around the periphery of the macula in this photograph are a series of small white spots. These are alterations to the tissue caused by laser exposure. The criterion for laser induced damage, in studies upon which MPEs are based, is the appearance of such a visible alteration. The retina is not uniform in

appearance but exhibits large and small scale variations in pigmentation. Because of this variation, the proportion of an incident laser beam absorbed by the tissue will not be the same for all exposure sites. If a series of retinal sites are subjected to laser exposure all at the same incident energy, not all will exhibit the same effect. Some sites will show visible alteration; some will not. For a given incident energy level, there will be a probability of alteration, computed by dividing the number of exposures producing alteration by the total number of exposures. When such an experiment is performed for a number of exposure levels, a curve is derived which relates the probability of alteration to the exposure level. The probability is low for low level exposures and high for higher level exposures. The data relating the probability of damage to the exposure energy can be processed by the statistical technique of probit analysis (3) to determine the incident energy having a fifty percent probability of producing alteration. This incident energy, or dose, is called the ED_{50}. The ED_{50} is not a damage threshold but rather a statistical point which has greater confidence than any other point on the dose-response curve. The MPE is the maximum permissible exposure for safe viewing of laser radiation. No alteration should ever occur upon exposure at the MPE, which therefore must be lower than the ED_{50}. Based on a number of considerations, the MPE has been chosen to be a factor of 10 to 100 below the ED_{50} upon which it is based. The variation of safety factor results from simplification of the dependence of MPE upon exposure parameters.

The most recent version of TBMED 279 was issued in 1975. At that time essentially no laser bioeffects data existed for the spectral range between 694.3 nm (ruby laser) and 1060 nm (neodymium laser). Faced with the absence of data, the writers of the standards chose to compute the MPE in this range by interpolation between the MPEs at 694.3 nm and 1060 nm. The interpolation was not arbitrary but was based on the transmission and absorption properties of ocular tissue. Figure 2 shows the relationship between the MPE and wavelength for the visible and near infrared. The ED_{50}s are also shown for some specific laser wavelengths, valid for ocular exposure to single short duration pulses. The MPE and ED_{50} are given in terms of total intraocular energy (TIE), that is, the total energy entering the eye. If the MPE is to be an accurate derivation of the ED_{50} for wavelengths between 694.3 nm and 1064 nm, the ED_{50} should closely follow a straight line between these wavelengths. The ED_{50} for 850 nm (erbium laser), recently obtained at LAIR (4), lies significantly below the expected value. Thus we have doubts about assumptions underlying the interpolated MPE in this spectral region. In light of this evidence, it became urgent to determine the wavelength dependence of ED_{50} near the GaAs wavelength of 900 nm.

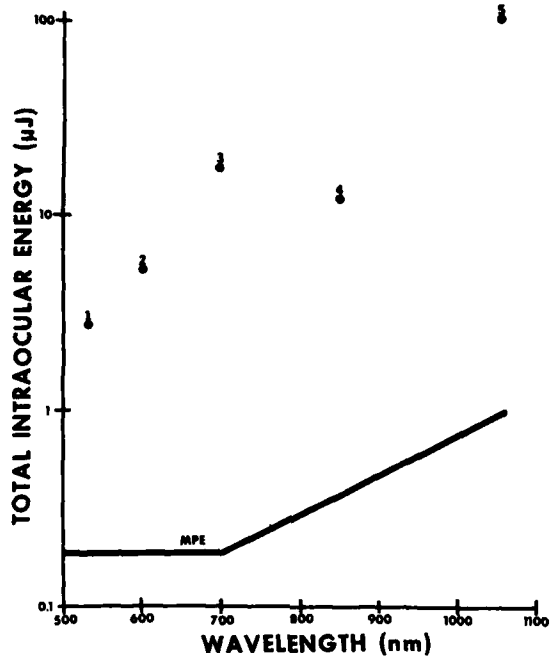

FIGURE 2. Wavelength dependence of the maximum permissible exposure (MPE) and the ED_{50} for retinal damage in rhesus monkey. Given ED_{50}s are for: 1 - 532 nm, 140 ns; 2 - 600 nm ,400 ns; 3 - 694.3 nm, 15 ns; 4 - 850 nm, 180 ns; 5 - 1064 nm, 180 ns

Advances in dye laser technology have made this study possible. The lasing medium of such a laser is a fluorescent dye carried in a suitable liquid solvent. When optically pumped with intense radiation from a flashlamp or laser, the dye can be caused to emit laser radiation at any wavelength within its fluorescent spectrum. The fluorescent bandwidth of most dyes is nanometers wide, and dyes are available which allow selection of any wavelength from the ultraviolet to greater than 900 nm.

The experiments and results of our studies with eyes of rhesus monkeys are reported in this document.

MATERIALS AND METHODS

The source of laser radiation in this study was a Molectron DL-18 dye laser coupled to a Molectron MY33 Nd:YAG laser. The neodymium laser

emitted 15 ns duration pulses at a repetition rate of 10 Hz and was provided with internal second and third harmonic generators which could be positioned so that the laser output was any of three wavelengths: 1064 nm (fundamental), 532 nm (second harmonic), or 355 nm (third harmonic). The output energy of the neodymium laser served as an excitation source for the dye laser which consisted of a side-pumped cell through which the dye was circulated, a diffraction grating which served as a wavelength tunable resonator mirror, and an output resonator mirror. The output wavelength of the dye laser was determined by the grating with the restriction that it be tuned to a wavelength within the fluorescent spectrum of the dye. The fluorescent spectrum of the dye in turn was dependent on the specific dye chosen, the dye solvent and concentration, and the excitation wavelength.

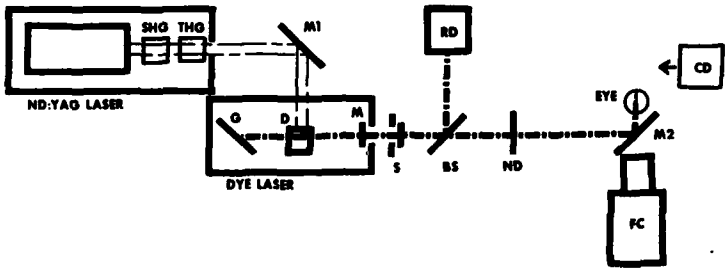

FIGURE 3. Exposure configuration.
BS - beamsplitter CD - calibrated detector for dosimetry
D - laser dye cell FC - fundus camera
G - diffraction grating for dye laser tuning
M - dye laser output mirror
M1 - redirecting mirror for Nd:YAG beam
M2 - dichroic mirror ND - neutral density attenuating filter
RD - reference detector S - shutter
SHG - second harmonic generator THG- third harmonic generator

Figure 3 is a schematic of the exposure system. The laser emitted a continuous train of pulses at 10 Hz; a shutter allowed selection of a single pulse for exposure. A beam splitter deflected a constant proportion of the pulse energy into a reference detector while the remainder of the energy passed through attenuators and onto a dichroic mirror. The mirror had high reflectivity at wavelengths longer than 700 nm but was transparent in the visible. A fundus camera, looking through the mirror, permitted observation of the retina to be exposed. The fundus camera, mirror, and laser beam were aligned so that the laser energy reflected by the mirror passed through the center of the ocular pupil and struck the retina at the site corresponding to the crosshairs of the fundus camera viewing optics. Before the rhesus monkey was positioned, a calibrated detector, which

directly read the incidence pulse energy, was placed so that it would receive all the energy that would normally enter the eye. The ratio of the energy at this position to the energy at the reference detector was obtained with the attenuator removed. Subsequently, when the eye was exposed, the energy entering the eye for each exposure was determined by multiplying the energy at the reference detector by the ratio previously determined and by the transmission of the attenuating filter chosen to give the desired energy. The laser wavelength, beam divergence, and pulse duration were determined for each wavelength. A Jarrell-Ash 1/2 meter spectrometer was used to measure the wavelength. The wavelength scale of the spectrometer was calibrated against a mercury spectral source; the subsequent laser wavelengths error was less than 0.1 nm. The beam divergence was measured by a linear detector array at the focal plane of a one meter lens.

Rhesus monkeys were used in this study. Each animal was sedated and anesthetized for exposure, its pupils were dilated, and the eye to be exposed was held open by a lid speculum. While the eye was open, the cornea was periodically irrigated with physiological saline solution to maintain clarity. For each test, an animal was positioned and 30 exposures were placed in an array in the extramacular retina. The initial exposures in each sequence were at a dose high enough to produce an immediate visible tissue response. Subsequent exposures were at successfully lower doses so that the range of doses in the array varied by about a factor of ten. The retina was photographed and the exposure sites marked on the photograph for subsequent identification. The exposure sites were examined by ophthalmoscope one hour after exposure and the presence or absence of visible alteration noted for each site. The response at each site was correlated to the dose at that site. For each wavelength, the data obtained by exposure of four to six eyes were statistically evaluated to determine the ED_{50} and associated 95% confidence limits. One animal, exposed to 900 nm radiation, was sacrificed one hour after exposure and the retinas prepared for histological evaluation.

RESULTS incident energy dose

The ~~ED_{50}~~ for single Q-switched exposure was determined for six laser wavelengths obtained from the dye laser. ~~The wavelengths and exposure conditions are listed in Table 1.~~ The solvent for all the laser dyes was DMSO. The laser linewidth at 912 nm was 0.4 nm. For the other wavelengths the laser linewidth was less than 0.08 nm, the resolution limit of the monochrometer used for wavelength measurements. The laser beam was nearly gaussian in profile. The beam divergence was measured at the diameter where the intensity fell to 1/e times the peak value. → p. 8

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TABLE 1
DYE LASER PARAMETERS

WAVELENGTH (nm)	PULSE DURATION (nsec)	BEAM DIVERGENCE (mrad)	DYE	CONCENTRATION (molar)	EXCITATION WAVELENGTH (nm)
850.2	11	1.4	DTTC	1.5×10^{-3}	532
			+ HIDC	1.1×10^{-3}	
859.6	10	1.6	IR144	6×10^{-4}	532
867.0	7	1.6	IR144	6×10^{-4}	532
880.0	14	1.4	IR125	1.8×10^{-4}	532
			+ HIDC	1.8×10^{-3}	
899.7	6	1.6	IR125	2×10^{-3}	355
912.0	7	1.6	IR140	3×10^{-3}	532

The ED_{50} for visible retinal alteration at one hour in rhesus monkey is given in Table 2 for each of these wavelengths. Also given are the 95% confidence limits about the ED_{50} and the slope of the regression line, defined as ED_{84}/ED_{50}. The data are for extramacular exposure.

TABLE 2
RETINAL ED_{50} FOR Q-SWITCH DYE LASER EXPOSURE IN RHESUS MONKEY

WAVELENGTH (nm)	ED_{50} (μJ)	95% LIMITS (μJ)	SLOPE
850.2	9.1	7.8-10.7	1.71
859.6	6.7	5.6-8.0	1.77
867.0	5.2	4.4-6.0	1.69
880.0	6.3	5.2-7.7	1.80
899.7	4.3	3.4-5.3	2.38
912.0	5.5	4.6-6.7	1.87

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Histologic evaluation

Retinal tissue from two eyes exposed to 900 nm radiation was processed and sectioned for light microscopy. Figure 4 is a retinal photograph of one eye taken just prior to sacrifice of the animal. Sites marked 1, 2, 3 and 5 were each exposed to a train of 100 pulses at 10 Hz. The energy per pulse in the train was 17 μJ. Between sites 1 and 2 and between sites 3 and 5 were placed 6 exposures, each consisting of a single pulse having an energy of 17 μJ. Figure 5 shows a section through one of the extramacular sites exposed to 100 pulses. The sensory retina is a complex tissue within which have been defined a number of layers. The retinal pigment epithelium (RPE) is a single layer of cells which contain the pigment melanin. Melanin is the strongest optical absorber in the retina; thus for most laser wavelengths, the RPE is the center of damage. Each photoreceptor of the retina extends through four layers, the outer segment layer (OS), the inner segment layer (IS), the outer nuclear layer (ON), and the outer plexiform layer (OP). The outer segment of the photoreceptor contains the photochemicals which convert the optical signal to a bioelectric signal, the inner segment and nucleus contain the life support system of the cell, and a nerve process extends into the outer plexiform layer where the bioelectrical signal is passed to other nerve cells which convey the information to the brain. Figure 5 shows that, although the damage to the RPE is slight, the photoreceptors at the exposure site have been damaged throughout their length.

retinal pigment epithelium

The retina contains two types of photoreceptors; the rods which respond to dim light, and the cones which respond to high ambient light and provide color vision. The two types of photoreceptors are not uniformly distributed in the retina: cones are more common in the macula and rods are more common in the extramacular retina. Figure 6 shows a lesion near the edge of the macula where both rods and cones are found. The dose producing this lesion was the same as that for Figure 5. The RPE is more extensively damaged in this lesion, and again the photoreceptors are damaged throughout their length. Figures 7 and 8 are magnified views of the lesions of Figure 5. It can be seen that although the rods are extensively damaged, the cones are relatively unaltered.

DISCUSSION

When the ED_{50} is plotted as a function of wavelength (Figure 9), a minimum is seen near 900 nm. This is difficult to explain on the basis of the known optical qualtities of the rhesus eye. Incident radiation must be absorbed by tissue to produce an alteration. A laser beam entering the eye passes through the cornea, aqueous, lens, and vitreous before reaching the retina. These transparent media absorb a fraction of the incident radiation. Of the radiation reaching the retinal surface, part is reflected and part transmitted through the retina. The remainder is

FIGURE 4. Photograph of rhesus monkey retina. The large white area is the optic disc and the dark area the macula. Tiny white spots (arrows) are focal 900 nm dye laser lesions. There are six barely visible lesions between arrows 1 and 2 and between arrows 3 and 5. Arrow 4 points to one of the lower level lesions.

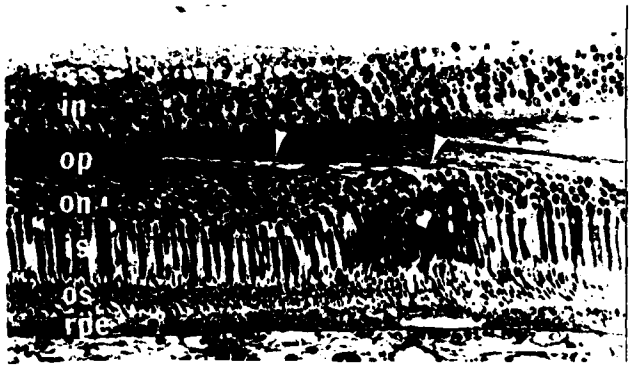

FIGURE 5. Light micrograph of lesion 2 of figure 1. The section shows the following layers of the retina: inner nuclear layer (IN); outer plexiform layer (OP); outer nuclear layer (ON); photoreceptor inner segments (IS); photorecptor outer segments (OS); retinal pigment epithelium (RPE). Small arrows indicate vacuolization. Dark stained nuclei are present in the RPE and ON. Some of the outer segments above the lesion are highly swollen. BAR = 100 µm.

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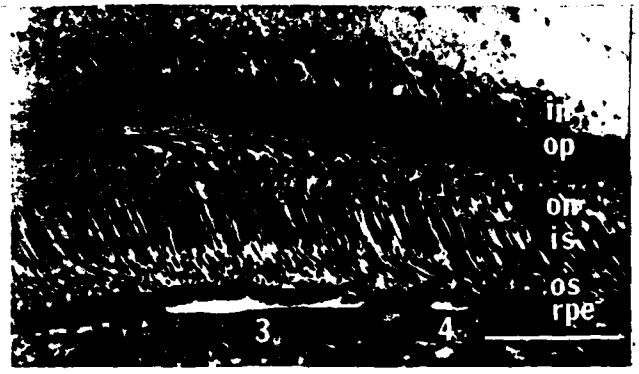

FIGURE 6. Light micrograph of lesions 3 and 4. Large vacuoles are present in the basal region of the RPE in both lesions and small vacuoles are present in the ON. Dark staining nuclei appear in the RPE and the ON. BAR = 100 µm

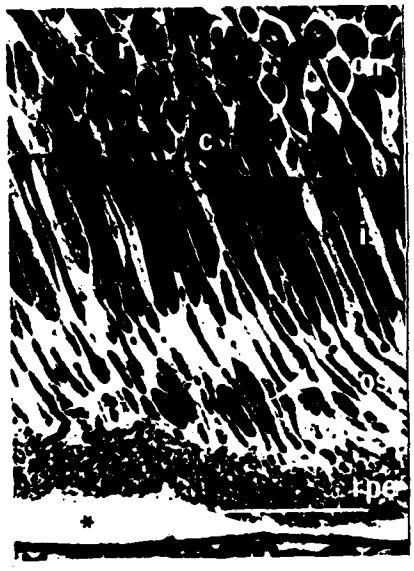

FIGURE 7. Light micrograph of lesion 3. A large vacuole (*) is seen in the basal region of the RPE. Melanin granules are clumped and disarrayed in this layer. Dark staining nuclei are present in the RPE as well as in the ON. Dark stained nuclei belong to rods (r), while cone nuclei (c) stain normally. The slender inner segments of rods are swollen and vacuolated while the larger cone inner segments are normal. BAR = 50 µm

FIGURE 8. Light micrograph of lesion 4. A vacuole (*) is present in the basal region of the RPE. Dark stained nuclei are present in the basal region of the RPE and one dark nucleus is present in the ON. The dark nucleus belongs to a rod (r) that has its outer segments near the lesion in the RPE. Inner segments of rods are highly swollen and vacuolated. The most severe vacuolation occurs at the junction of IS and OS (large arrow) adjacent to the high energy lesion. The cone (c) outer segments show whorl formation about midway in their lengths. BAR = 50 µm

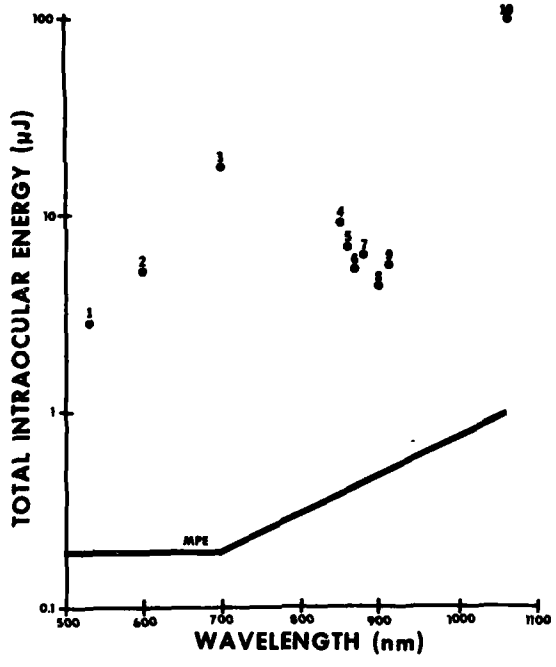

FIGURE 9. Wavelength dependence of the MPE and the ED_{50} for retinal damage in rhesus monkey. Given Ed_{50}s are for:

1- 532 nm, 140 ns	6 - 867 nm, 7 ns
2 - 600 nm, 400 ns	7 - 880 nm, 14 ns
3 - 694.3 nm, 15 ns	8 - 899.7 nm, 6 ns
4 - 850.2 nm, 11 ns	9 - 912 nm, 7 ns
5 - 859.6 nm, 10 ns	10 - 1064 nm, 180 ns

absorbed in the retinal tissue. Absorption and reflection by the ocular media are wavelength dependent quantities which have been measured by several investigators (5-7). From these data, the energy absorbed in the retina at each wavelength can be computed as a fraction of the energy incident at the cornea. A transformation of this relationship provides the relative energy at the cornea as a function of wavelength to produce constant absorbed energy in the retina (Figure 10). Comparing this result to the bioeffects data for 850 nm to 900 nm, we are driven to consider two possibilities: either there is a flaw in the ocular absorption measurements; or laser radiation in this spectral range produces retinal alteration with lower absorbed energy. The optical absorption measurements of the rhesus eye were performed in vitro with low level illumination.

These measurements would not detect absorption mechanisms which operate only in living tissue nor would they detect power dependent interactions. Photochemical interactions, normally associated with shorter wavelengths and longer exposure durations, require lower energy for initiation than do the thermal interactions normally associated with near infrared retinal alteration. The retina is a beehive of photochemical and biochemical processes which might be altered by specific wavelengths. The histopathology suggests that 900 nm radiation is absorbed by the rod photoreceptors to the extent that the underlying RPE is relatively spared in the rod-rich areas of the retina. The data currently available are not sufficient to explain the reduced ED_{50} near 900 nm.

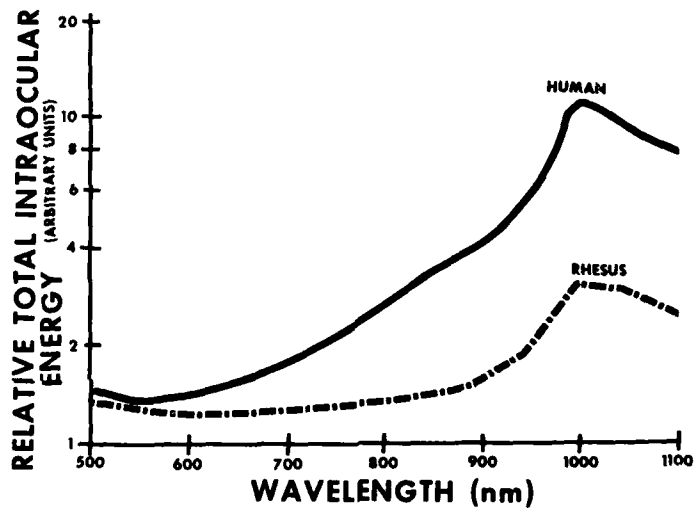

FIGURE 10. Wavelength dependence of the total intraocular energy required to produce a constant level of absorbed energy in the retina of human and rhesus monkey eyes.

The determination of ED_{50}s is not an exact science; the shape of the ED_{50} versus wavelength relationship from 700 nm to 1060 nm may not be exactly represented by the data of Figure 9. However, the data are internally consistent in that all the data were collected at LAIR by the authors and have a commonality of dosimetry and determination of results. All the ED_{50}s of Figure 9 are for single short pulse exposure to the extramacular retina in rhesus monkey. There is a real decrease in the ED_{50} between 850nm and 900 nm as compared to the ED_{50}s at 700 nm and 1060 nm. The MPE as provided in TBMED 279 is not consistent with these new bioeffects data. When the MPE at 900 nm was compared to the data of this experiment, we found a safety factor of 10. The current MPE should provide

adequate protection for exposure to single pulses from the GaAs laser.

CONCLUSIONS

The MPEs for wavelengths affecting GaAs laser training devices were derived based on assumptions concerning interaction of laser radiation with retinal tissue. The data of this study show that those assumptions were not adequate, and that retinal damage occurs at lower doses than expected. The results of this study do not necessarily have an adverse affect on the use of GaAs laser training devices - the safety standards still provide an adequate safety margin. The bioeffects data base in this spectral region is still incomplete; additional data now being collected will serve to define the wavelength dependence of ED_{50} between 700 nm and 1060 nm. It is possible that, when the data base is complete, a recommendation will be made to change the operating wavelength of training devices to a wavelength with increased safety margin. The data currently available do not warrant a recommendation for modification of the safety standards.

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In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals" as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboritory Animal Resources, National Academy of Sciences, National Research.

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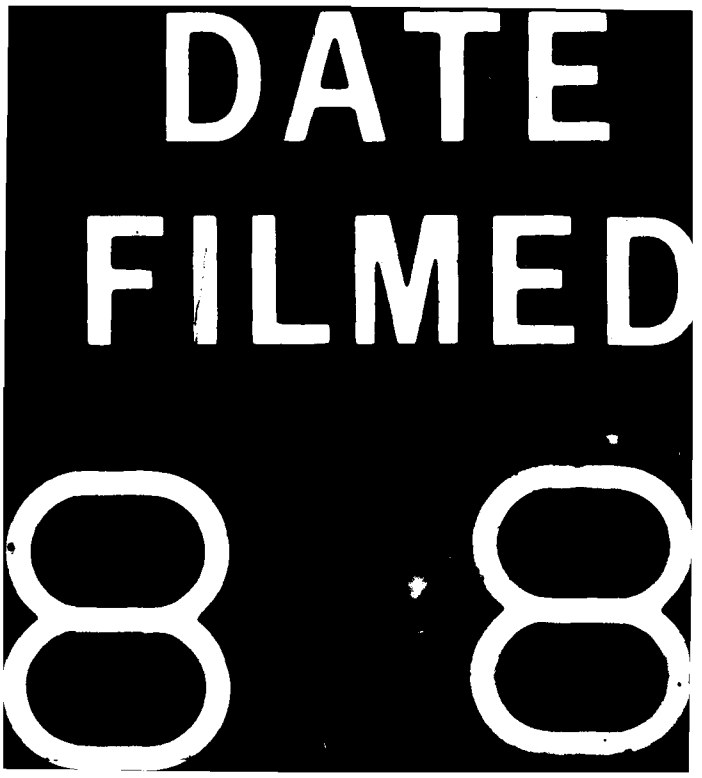
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